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Effects of Disinfectants in Renal Dialysis Patients

by Elias Klein*

Patients receiving hemodialysis therapy risk exposure to both disinfectants and sterilants. Dialysis equipment is disinfected periodically with strong solutions of hypochlorite or formaldehyde. More recently, reuse of dialyzers has introduced the use of additional sterilants, such as hydrogen peroxide and peracetic acid. The use of these sterilants is recognized by the center staffs and the home patient as a potential risk, and residue tests are carried out for the presence of these sterilants at the ppm level. Gross hemolysis resulting from accidental hypochlorite infusion has led to cardiac arrest, probably as a result of hyperkalemia. Formaldehyde is commonly used in 4% solutions to sterilize the fluid paths of dialysis controllers and to sterilize dialyzers before reuse. It can react with red cell antigenic surfaces leading to the formation of anti-N antibodies. Such reactions probably do not occur with hypochlorite or chloramines.

The major exposure risk is the low concentration of disinfectant found in municipal water used to prepare 450 L dialysate weekly. With thrice-weekly treatment schedules, the quality requirements for water used to make this solution must be met rigorously. Standards for water used in the preparation of dialysate have recently been proposed but not all patients are treated with dialysate meeting such standards. The introduction of sterilants via tap water is insidious and has led to more pervasive consequences. Both chlorine and chloramines, at concentrations found in potable water, are strong oxidants that cause extensive protein denaturation and hemolysis. Oxidation of the Fe^{2+} in hemoglobin to Fe^{3+} forms methemoglobin, which is incapable of carrying either O_2 or CO_2. Chloramine can form not only methemoglobin, but can also denature proteins within the red cell, thus forming aggregates (Heinz bodies). Chloramines also inhibit hexose monophosphate shunt activity, a mechanism that makes the red cell even more susceptible to oxidant damage.

These risks can only be minimized through close cooperation between the clinical staffs and the water carrier's technical personnel.

Introduction

In mid-1985 there were 78,500 patients in the United States suffering from end stage renal disease (ESRD) requiring supportive dialysis therapy. Of this number, 66,600 were treated by hemodialysis, 62,500 were treated in centralized facilities, and 4,100 were treated at home. Hemodialysis treatment typically consists of a 4-hr dialysis, during which time an electrolyte solution (dialysate) flows countercurrent to the patient's blood, separated from the latter only by approximately one square meter of an 8 to 11 μm thick cellulose membrane. A schematic of the flow path is shown in Figure 1.

During the course of the treatment, the patient's blood is equilibrated with approximately 120 L of dialysate, prepared by metering a concentrated salt solution into tap water purified for this purpose (water for dialysate). The patient, therefore, is exposed to 70 to 80 times the normal daily water intake (1.5–2 L/day). Moreover, all of the low molecular weight constituents of potable water—many of which cannot cross the gastrointestinal barrier—can be transferred into the circulation of the hemodialysis patient. Many of these solutes may not be considered toxic as they are not normally absorbed. Because of the possibility of direct diffusion into the patient's serum, such potentially toxic substances must be removed from the water supply before the dialysate is formulated. These substances include the flocculating agents used to settle turbidity, transition elements, and all sterilants or disinfectants used to control biological burdens.

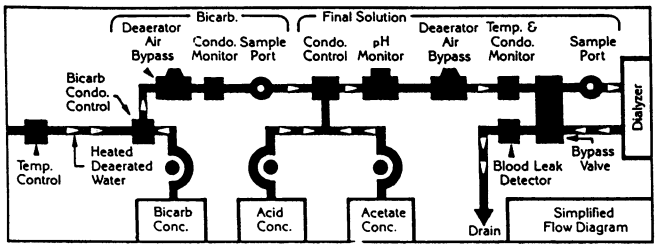

FIGURE 1. Flow diagram of typical dialysate preparation system.

The determination of permissible toxic burdens for these patients is an on-going effort, made more difficult by the complications of the underlying diseases present in the ESRD population. Currently, there are standards

*University of Louisville, School of Medicine, Kidney Disease Program, University of Louisville, Louisville, KY 40292.

Table 1. Hemodialysis water quality—chemical contaminant levels.

Contaminant	Suggested maximum level, mg/L
Calcium	2 (0.1 mEq/L)
Magnesium	4 (0.3 mEq/L)
Sodium[a]	70 (3 mEq/L)
Potassium	8 (0.2 mEq/L)
Fluoride	0.2
Chlorine	0.5
Chloramines	0.1
Nitrate (N)	2
Sulfate	100
Copper, barium, zinc	each 0.1
Aluminum	0.01
Arsenic, lead, silver	each 0.005
Cadmium	0.001
Chromium	0.014
Selenium	0.09
Mercury	0.0002

[a] 230 mg/L (10 mEq/L) where sodium concentration of the concentrate has been reduced to compensate for the excess sodium in the water, as long as conductivity of the water is being continuously monitored.

for hemodialysis systems, which were prepared in 1981 by committees of the Association for the Advancement of Medical Instrumentation (AAMI) (*1*). The section applicable to the preparation of water for dialysate is shown in Table 1. Note that the preponderance of concern is with inorganics; only chlorine and chloramine are listed in the category of sterilants or disinfectants.

Disinfectants and Sterilants

The home hemodialysis patient and dialysis center support staff must deal with both sterilants and disinfectants to reduce bacterial burdens in the fluid pathway of their respective dialysis equipment. Most patients are served by municipal water carriers who provide bacterial control through either chlorine or chloramine in the water reaching the dialysis facility, whether in the home or centrally located. These oxidants must be removed from the water used for dialysis for reasons to be cited later. Between the point of removal of the chlorine compound(s) and the actual dialysis step, the fluid path of the machinery can, and does, harbor bacterial cultures. These bacterial burdens may be aggravated by the presence of sand filters, carbon adsorption beds, and other water-treating equipment interposed between the supply line and the dialysate controllers. To manage the inevitable bacterial contamination, dialysis equipment manufacturers recommend daily disinfection and periodic sterilization.

The most commonly used disinfectant is a basic solution of sodium hypochlorite. A 0.25% solution is circulated through the fluid pathways, followed immediatedly by extensive rinsing with water for dialysis. The washing is continued until the effluent concentration is reduced below 0.5 ppm active chlorine. Hemodialysis controllers are also sterilized, typically on a biweekly basis, using 3.75% formaldehyde exposure for at least 16 hr. The entire fluid pathway must be rinsed after sterilization until the effluent concentration of formaldehyde is less than 5.0 ppm.

In many hemodialysis facilities, it is now common practice to submit dialyzers to a reuse procedure in which the adhering blood products are washed out of the dialyzer and the cleansed dialyzer is sterilized by storage in one of several sterilants until just before use. The most commonly used sterilant is 4% formaldehyde solution; a mixture of peracetic acid and hydrogen peroxide is also used, but experience with this solution is less extensive. When formaldehyde is used as the dialyzer sterilant, an intermediate wash step containing sodium hypochlorite may be used to solubilize adhering protein through oxidation. The peroxide solutions do not require additional oxidative denaturation of adhering protein.

All these sterilants must be removed not only from the dialyzer fluid pathways, but also from the plastic materials into which they may have diffused. Otherwise, traces of sterilant may be dialyzed into the patient's blood stream with the same ease as metabolic products dialyzed out of the blood stream.

Systemic Effects of Sterilants and Disinfectants

Sodium Hypochlorite

An accidental systemic exposure of a patient to high concentrations of sodium hypochlorite was reported by Hoy (*2*). In the reported accident, the disinfection procedure of the dialysate controller was begun before the patient had completed treatment. An estimated dose of 30 mL of 3% hypochlorite was transferred to the patient, based on changes in serum electrolyte levels. Immediate hemolysis of the patient's blood resulted in a doubling of serum potassium concentration to 7.0 mEq/L. The hyperkalemic levels resulted in cardiac arrest. The rise in serum potassium is consistent with rapid degradation of the erythrocyte, as reported by Baker (*3*).

Monochloramine

A number of studies reporting the effects of chloramine on blood components have been reported in the last few years (*4–8*). Two major effects are observed. The first is oxidation of hemoglobin to methemoglobin in direct proportion to the chloramine concentration (*9*). Free chlorine, although an equally strong oxidant, does not produce methemoglobin. A second consequence is the denaturation of hemoglobin to form insoluble Heinz bodies (*8*) within the red cells. In addition to the oxidative damage caused directly by chloramines, the effect is magnified by the inhibition of repair mechanisms. The hexose monophosphate shunt normally reduces nicotinamide adenine dinucleotide phosphate (NADPH), which protects the red cells against oxidative damage. Prior exposure of red cells to chloramines inhibits this

protective mechanism, subjecting the cells to even more severe damage on subsequent exposure to chloramine.

Current awareness of the dangers of chloramine exposure has been raised by standards introduced during 1985 by the California Department of Health (*10*). As a consequence of chloramination of domestic water supplies in southern California, a number of hemolytic events were reported. Chloramination was stopped in December 1984 until new regulations requiring dialysis facilities to remove chloramine from their water supplies could be promulgated. Since early 1985, all California hemodialysis units operate under guidelines requiring removal and testing for chloramine levels in water used for dialysis. Unfortunately, many other areas of the country, in the process of switching from chlorine to chloramine to meet EPA trihalomethane level guidelines, may not provide adequate warning to permit hemodialysis centers to deal with the presence of chloramines (Ronald L. Wathen, personal communication).

Formaldehyde

Formaldehyde at high concentrations poses a risk of acute toxicity. However, at trace levels, a chronic effect has been identified in the hemodialysis patient population. Erythrocytes can be characterized in terms of MN phenotypes, analogous to the AB-O system. The normal distribution of MM, NN, and MN phenotypes is approximately 25%, 25%, and 50%, respectively. Only 25% of the population would be expected to have anti-N antibodies. However, patients exposed chronically to trace levels of formaldehyde (by formalin sterilization of their dialyzers to permit reuse) are reported to develop anti-N-like antibodies, probably as a result of reaction with the dissolved form of formaldehyde, methylene glycol. The occurrence of this antibody has been implicated in renal allograft failure (*11*). The anti-N-like antibodies are formed following exposure to sodium hypochlorite; no data are reported for the formation of the antibodies in response to chloramine exposure.

Peroxides

The action of strong oxidants, such as hydrogen peroxide and peracetic acid, is expected to be immediate and directed at protein oxidation. The literature does not currently contain reports linking chronic exposure to these oxidants with any systemic effects.

Conclusion

The use of sterilants and disinfectants to reduce bacterial burdens in hemodialysis equipment is a necessary consequence of unwanted infections of the fluid pathways. The biocides introduced both by the water carrier supplying the hemodialysis facility and those used to maintain the equipment pose a serious risk to the patient. Chronic, subacute exposures have been shown to damage a number of erythrocyte and plasma protein functions. Damage includes shortened red cell life, development of autoimmune antibodies, and denaturation of serum proteins.

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